Treatment of Severe Hyponatremia

Richard H. Sterns

Abstract

Patients with severe (serum sodium ≤120 mEq/L), symptomatic hyponatremia can develop life-threatening or fatal complications from cerebral edema if treatment is inadequate and permanent neurologic disability from osmotic demyelination if treatment is excessive. Unfortunately, as is true of all electrolyte disturbances, there are no randomized trials to guide the treatment of this challenging disorder. Rather, therapeutic decisions rest on physiologic principles, animal models, observational studies, and single-patient reports. European guidelines and recommendations of an American Expert panel have come to similar conclusions on how much correction of hyponatremia is enough and how much is too much, but there are important differences. We review the evidence supporting these recommendations, identifying areas that rest on relatively solid ground and highlighting areas in greatest need of additional data.

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University of Rochester School of Medicine and Dentistry, Rochester General Hospital, Rochester, New York

Correspondence:
Dr. Richard H. Sterns, Rochester General Hospital, 1425 Portland Avenue, Rochester, NY 14621. Email: richard.sterns@rochesterregional.org

Introduction

With the publication of two sets of rather similar consensus guidelines from both sides of the Atlantic (1,2), a quarter century of bitter controversy has yielded to general agreement on how to manage severe hyponatremia (sodium ≤120 mEq/L). To appreciate the change that this entails, consider a patient whose sodium is 100 mEq/L; a nephrologist adhering to current guidelines might bring the concentration up to 128 mEq/L over 6 days (3)—ten times more slowly than one adhering to widely accepted conventional wisdom of the 1980s (4). It was once believed that, to avoid lethal complications, rapid correction to a safe level above 128 mEq/L was essential (4,5). Much slower correction is now recommended to avoid the osmotic demyelination syndrome, a complication of excessive treatment (1,2,5–7).

What evidence supports this dramatic change? Unfortunately, as is true for all electrolyte disturbances, no randomized, controlled trials exist; rather, we must rely on physiology, experimental models, observational studies, and single-patient reports. This review will visit that evidence to identify therapeutic recommendations resting on relatively solid ground and highlight areas needing additional data.

Physiology and Experimental Models

Lowering plasma sodium below 120 mEq/L within hours causes severe cerebral edema (7–9). Rapid correction with hypertonic saline ameliorates brain swelling and prevents fatal herniation. If sublethal hyponatremia persists, the brain restores its volume without help from hypertonic saline. Brain cells adapt by exporting electrolytes rapidly and organic osmolytes more slowly (24–48 hours), so that extracellular and intracellular osmolalities remain equal without increasing cell volume; these adaptations permit survival with minimal brain swelling (9,10). However, because cellular reuptake of organic osmolytes can take up to a week, the adaptation makes brain cells susceptible to injury from a rapidly rising plasma sodium (11). After <24 hours of hyponatremia, rapid correction is well tolerated, but after ≥3 days, the same therapy results in osmotic demyelination (10). In dogs, experimental lesions closely mimic those in humans (12). Untreated hyponatremia does not induce osmotic demyelination (11), and although hypoxia is a proposed cause, depriving hyponatremic rats of oxygen does not reproduce the disease (13). Within 12 hours after rapid correction, protein aggregation, DNA fragmentation, and markers of programmed cell death develop in astrocytes; the injury evolves, culminating in destruction of myelin (14). Osmotic demyelination can be prevented by relowering plasma sodium within 12 hours after rapid correction (9,13,15).

On the basis of these experimental observations, hyponatremia present for >48 hours is deemed "chronic," whereas a more abrupt onset with shorter duration is called "acute." Fatal brain damage in untreated acute experimental hyponatremia is caused by cerebral edema; demyelinating brain lesions in chronic hyponatremia are complications of excessively rapid correction.

Challenges in Translating Experimental Observations to the Bedside

Observational studies in humans mirror findings in experimental models. Almost all reports of death from cerebral edema are in untreated acute hyponatremia from self-induced water intoxication (psychosis, intense exercise, and use of "Ecstasy") and postoperative intravenous fluids; rapid correction in these

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settings is generally well tolerated (2,4,5,16–18). Almost all reports of osmotic demyelination are in patients who became gradually hyponatremic at home; slow correction avoids these complications (2,5,16–18). The validity of these general principles has withstood scrutiny for over 25 years; however, challenges remain in translating them to evidence-based recommendations that can be applied at the bedside.

Acute Versus Chronic Hyponatremia

The designations "acute" and "chronic" hyponatremia do not always work well in practice. Many physicians are confused by the terms, believing "chronic" to mean hyponatremia that has been present for months and "acute" to mean hyponatremia that has recently become symptomatic. Even when currently accepted time-based definitions (>48 hours = chronic; <48 hours = acute) are understood, the true duration of hyponatremia is seldom known. In symptomatic chronic hyponatremia, the possibility of an acute exacerbation raises concerns for seizures or even herniation. Conversely, despite a history of severe polydipsia, the possibility of underlying chronic hyponatremia raises concern for osmotic demyelination if correction is excessive.

These uncertainties were much more troublesome when it was believed that rapid correction to 120 or even 128 mEq/L was needed to ensure survival and avoid hypoxic brain damage; it appeared then that patients with extremely low serum sodium concentrations would be harmed by treatment that was either too slow or too fast (5). If only a small increase in serum sodium is needed, a distinction between acute and chronic hyponatremia may be unnecessary.

Like any therapeutic endeavor, treatment of symptomatic hyponatremia must be sufficient to prevent complications of untreated disease, while avoiding harmful, excessive therapy. The therapeutic window between benefit and harm is our treatment goal. To define this therapeutic window, we must seek evidence of how much correction of hyponatremia is "enough" and how much is "too much."

How Much Correction Is Enough?

Defining appropriate treatment for life-threatening cerebral edema is difficult, because it is seldom seen in observational studies. The rarity of fatal cerebral edema should not provide comfort to clinicians treating an individual patient. Death and major morbidity from acute hyponatremia may be rare, because only a small percentage of patients become hyponatremic over a few hours. Morbidity and mortality are still a risk if serum sodium has fallen rapidly (16).

Acute hyponatremia often presents with seizures and coma, which are thought to reflect cerebral edema. A handful of published cases of patients provide data for the first few hours after successful treatment; they suggest that rapid correction by 4–6 mEq/L is enough to stop hyponatremic seizures (5).

Given the relationship between intracranial pressure and volume, a small increase in serum sodium should have a major effect. After a critical threshold is reached, a few milliliters of additional intracranial volume increases intracranial pressure precipitously; similarly, a small decrease in volume achieved by osmotherapy reduces intracranial pressure precipitously (19). In normonatremic patients who are treated for severe cerebral edema in neurocritical care units, raising serum sodium by 5 mEq/L with hypertonic saline is enough to markedly reduce intracranial pressure and reverse impending herniation (5,9,20). Advice to "half correct" hyponatremia within 12–24 hours or raise serum sodium to a "safe" level above 120 or 128 mEq/L is unsupported by any evidence that this is necessary.

Because of referral bias, published reports of deaths and neurologic disability from hyponatremic encephalopathy cannot be used to define adequate therapy. Referral bias is a specific type of selection bias that occurs when the likelihood of unusual outcomes is increased because of referrals to a study; it can result in erroneous conclusions when results in the referred population are compared with results in an unselected population (21). Series reporting fatalities from hyponatremia are collections of individual patients treated in multiple medical centers referred for an expert opinion regarding causation (22,23). Because an unusual adverse outcome was the reason for referral and because herniation preceded treatment, these series cannot define the true risks of symptomatic acute hyponatremia or a minimum limit for correction. However, correction rates in patients referred after an adverse outcome have been compared with correction rates and outcomes in patients actually treated for hyponatremia by the authors (23). The comparison is invalid.

Some authors have correlated correction rates of hyponatremia to mortality, concluding that inadequate treatment increases the risk of dying (24–27). However, mortality can be a very misleading outcome measure.

Most patients dying in the hospital with hyponatremia succumb to their underlying disease; deaths from cerebral edema are quite uncommon. A 12-year review of all hospital deaths associated with serum sodium <120 mEq/L identified only one death from cerebral edema (0.15% of patients) (28). A 16-year Mayo Clinic survey of 290,815 surgical procedures on women failed to identify a single patient with respiratory or cardiac arrest due to postoperative hyponatremia (29).

Correction rates are affected by the underlying cause (30,31). Hyponatremia due to heart failure, cirrhosis, kidney injury, or malignancy does not spontaneously resolve and may not be treated; patients with these disorders often die in the hospital. By contrast, hyponatremia caused by diuretics or antidepressants resolves after medications are discontinued; patients with medication-induced hyponatremia rarely die in the hospital.

Lower serum sodium concentrations are associated with more rapid correction rates (30–32). Paradoxically, the lowest serum sodium levels are associated with the lowest mortality; hospitalized patients with very low serum sodium levels are more likely to have been admitted for medication-induced hyponatremia, and patients with milder hyponatremia are more likely to have been hospitalized for severe, potentially fatal illness (28,30,31).

How Much Correction Is Too Much?

Too much correction of chronic hyponatremia causes osmotic demyelination. Although sometimes called rare, it is actually more common than herniation from untreated acute hyponatremia. There are several single-center series of osmotic demyelination documented by autopsy or magnetic resonance imaging (MRI) (Table 1) (33–38). In the 16-year Mayo Clinic survey that found no patients with fatal postoperative hyponatremia, six patients with osmotic demyelination were identified (29); in another 11-year survey, the Mayo Clinic identified 18 patients with MRI-documented demyelination associated with hyponatremia (33). One large hospital in India identified eight patients with MRI-documented demyelination in a single year; in five, serum sodium was ≤105 mEq/L, and in one, it was <110 mEq/L (38).

Although osmotic demyelination is common enough to be studied in individual centers, except for patients with liver transplants who are unusually susceptible (39), only a small percentage of patients with serum sodium <120 mEq/L is affected. The infrequency of osmotic demyelination should not provide comfort to clinicians treating individual patients. Post-therapeutic neurologic complications are especially common with extremely low serum sodium concentrations; at a sodium <105 mEq/L, they affect >50% of rapidly corrected patients (6,17,18) (Figure 1). Osmotic demyelination may be considered rare, because serum sodium levels <105 mEq/L are rare.

Osmotic demyelination syndrome describes a biphasic sequence of events (6). Symptoms (usually moderate but occasionally severe) from untreated hyponatremia initially resolve as serum sodium rises followed days later by new progressive neurologic findings (seizures, behavioral disturbances, swallowing dysfunction, paralysis, or movement disorders). The clinical syndrome is associated with demyelinating lesions in the central pons (central pontine myelinolysis) and often accompanied by similar symmetrical lesions outside the pons (extrapontine myelinolysis).

In early reports, patients with the typical biphasic neurologic illness that we now call osmotic demyelination syndrome had lesions confirmed by autopsy; however, most patients with osmotic demyleination syndrome do not die

Table 1. Large single-center series of patients with osmotic demyelination (autopsy or magnetic resonance imaging)

Author (Ref.), Year; Institution	Years of Study	Total No. of Patients	Patients with Hyponatremia	Serum Na in Patients with Hyponatremia Mean (Range), mEq/L	Documented Rapid Correction	Increase in Na in 24 h, mEq/L	Increase in Na in 48 h, mEq/L
Graff-Radford *et al.* (33), 2011; Mayo Clinic, the United States	1999–2010	24	18	114 (96–129)	16	Not provided	Median, 21; range, 10–28
Odier *et al.* (34), 2010; University of Montreal, Canada	1995–2007	12	6	106 (97–116)	6	7, 10, 23, 15, 40, 23	21, 28, 30, 19
Kallakatta *et al.* (35), 2011; Chitra Institute, India	1999–2008	25	20	108 (91–130)	12	>8 mEq/L per day	Not provided
Menger and Paehge (37), 1999; University of Witten, Germany	1990–1996	44	21	108 (99–121)	21	Mean 14.4	Not provided
de Souza and Desai (38), 2012; Goa Medical College, India	2010	8	8	104 (95–122)	8	9.9, 11.2, 22, 14, 13, 17, 14, 20	16.5, 19, 27, 16,17, 28, 21, 31; from personal communication (A. de Souza)
Karp and Laureno (36), 1993; Washington Medical Center, the United States	1993	14	14	104 (91–110)	14	>18 in 11 patients + 9 (23 in 35 h), 10, 12	>18

Na, sodium.

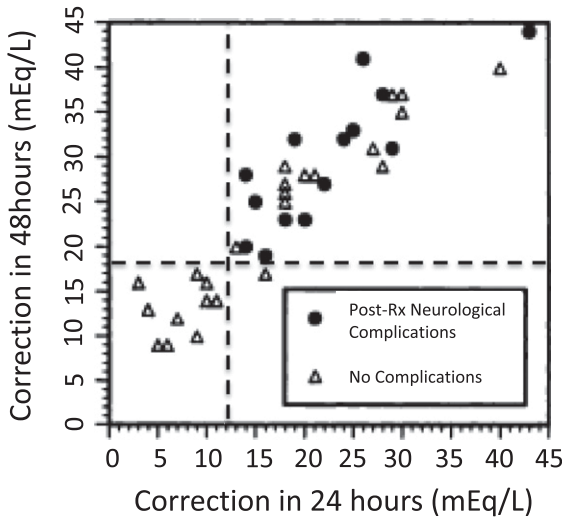
Correction in 48hours (mEq/L)
0 5 10 15 20 25 30 35 40 45
Correction in 24 hours (mEq/L)
0 5 10 15 20 25 30 35 40 45
Post-Rx Neurological Complications
No Complications

Figure 1. | In a cohort of chronically hyponatremic patients with serum sodium concentrations ≤105 mEq/L, post-therapeutic (post-Rx) neurological complications occurred after correction by >12 mEq/L in 24 hours and >18 mEq/L in 48 hours. Patients with chronic hyponatremia refers to patients without psychotic polydipsia who became hyponatremic at home. Solid circles represent patients with post-therapeutic neurologic complications, and open triangles represent patients who recovered uneventfully. The dashed lines represent therapeutic limits identified by the study (12 mEq/L in 24 hours and 18 mEq/L in 48 hours). Modified from ref. 18, with permission.

(40). MRI can identify lesions of osmotic demyelination in living patients, but the images must be properly timed. When symptoms first appear, restricted diffusion on MRI may be sensitive enough to detect lesions; however, the initial MRI is usually normal, and images become positive 1–3 weeks later (41). Both clinical and imaging findings are reversible, and some patients improve after a brief period of neurologic disability and never develop a positive MRI (Figure 2) (42). Patients with the typical course of osmotic demyelination syndrome but normal brain MRI may not be found in retrospective surveys without meticulous chart review.

Observational studies of patients with serum sodium ≤120 mEq/L have shown that post-therapeutic neurologic complications are significantly more common after rapid correction rates (Table 2) (6,16–18,43–46). However, because studies were small, used different criteria to define correction and neurologic injury, and reported serum sodium at inconsistent intervals, they can only provide a rough estimate of how much correction is too much.

There are many published patient series of MRI or autopsy-defined osmotic demyelination and hundreds of single-patient reports; serum sodium values and correction rates are not always included (40). Rapid correction of hyponatremia is not the sole cause of central pontine myelinolysis; other causes include hypernatremia, severe hyperglycemia, malignancy, and hyperammonemia.

Autopsy- or MRI-defined cases represent the most severe end of the spectrum of injury caused by excessive correction. More subtle injury is more difficult to identify and may occur at less rapid correction rates. However, because rapid correction of hyponatremia is not the sole cause of autopsy- or MRI-defined lesions, it may not be appropriate to ascribe them to changes in serum sodium concentration if clinical features of osmotic demyelination syndrome are absent.

Evidence Supporting Current Recommendations

Emergency Interventions

The European consensus guidelines and American expert panel both recommended bolus infusion of 3% saline

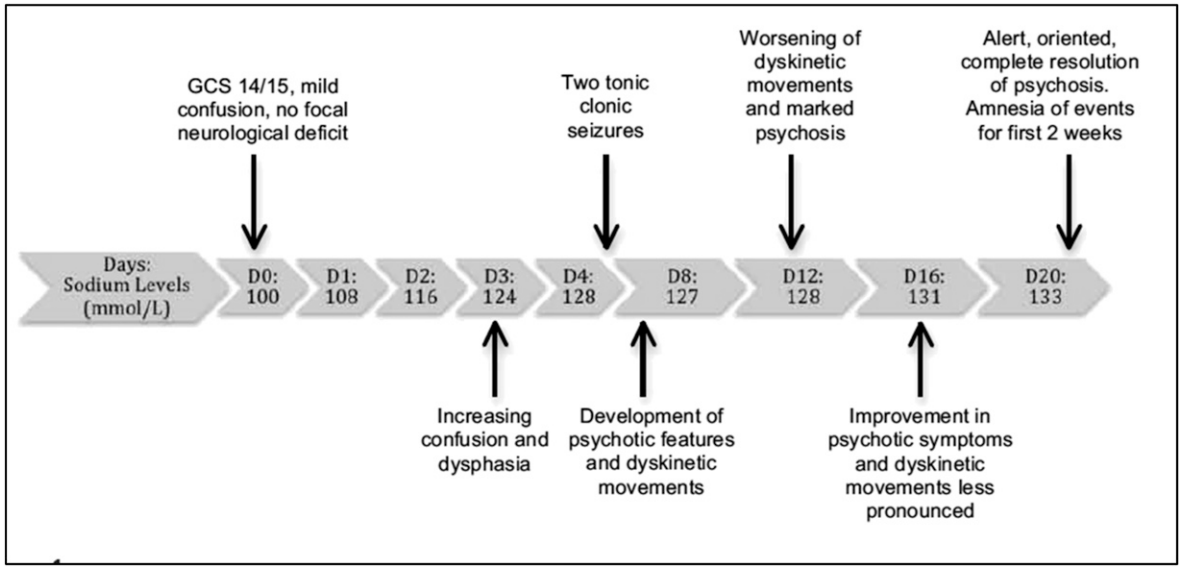
GCS 14/15, mild confusion, no focal neurological deficit
Two tonic clonic seizures
Worsening of dyskinetic movements and marked psychosis
Alert, oriented, complete resolution of psychosis. Amnesia of events for first 2 weeks
Days: Sodium Levels (mmol/L)
D0: 100
D1: 108
D2: 116
D3: 124
D4: 128
D8: 127
D12: 128
D16: 131
D20: 133
Increasing confusion and dysphasia
Development of psychotic features and dyskinetic movements
Improvement in psychotic symptoms and dyskinetic movements less pronounced

Figure 2. | Limits for safe correction are difficult to define when the serum sodium concentration is extremely low. This patient presented with mild symptoms despite a serum sodium of 100 mEq/L. Beginning on the third day after correction by 8 mEq/L per day, the patient developed new progressive symptoms, including dysphasia, psychosis, and dyskinetic movements consistent with a diagnosis of osmotic demyelination syndrome. However, the symptoms resolved spontaneously, and magnetic resonance imaging was negative. D, day; GCS, Glascow coma scale. Reprinted from ref. 42, with permission.

Table 2. Correction rates and outcomes of hyponatremia reported in observational cohort studies

Author (Ref.), Year, Type of Study	No. of Patients Studied	Serum Na, (mEq/L)	Criteria	Patients with Osmotic Demyelination Syndrome	ΔNa With and Without Osmotic Demyelination Syndrome
Sterns (17), 1987, Retrospective two hospitals	54	≤110	Admitted from home with chronic[a] hyponatremia	7 Clinical diagnosis	>0.55[b] versus ≤0.55 mEq/L per hour $P<0.02$
Brunner *et al.* (43), 1990, Prospective single center	13	<115	Admitted from home with hyponatremia	3 MRI diagnosis	30 versus 18 mEq/L per 24 h $P<0.05$
Tanneau *et al.* (45), 1994, Retrospective single center	12	≤115	Admitted patients with compulsive water drinking	5 Clinical diagnosis	21.8 versus 15.5 mEq/L per 24 h $P<0.02$
Ellis (44), 1995, Prospective two hospitals	158	≤120	All admitted patients	9 Clinical examination by single neurologist	12.1 versus 8.2 mEq/L per 24 h $P=0.01$
Sterns *et al.* (18), 1994, ¼ Prospective; ¾ Response to questionnaire multicenter	64	≤105	All admitted patients	11 Clinical diagnosis 3 MRI diagnosis All chronic cases[a]	>12 versus ≤12 mEq/L per day $P=0.02$[c] >18 versus ≤18 mEq/L per 48 h $P=0.02$[d] >0.55[b] vs ≤0.55 mEq/L per hour $P=0.01$[e]
Vu *et al.* (46), 2009, Retrospective two hospitals	255 (37 corrected by >12 mEq/L in 24 h)	≤120	Admitted from home with hyponatremia	4 MRI diagnosis	>12 vs ≤12 mEq/L per day $P=0.06$

Na, sodium; MRI, magnetic resonance imaging.
[a]Chronic defined as patients without psychotic polydipsia who became hyponatremic at home.
[b]Average rate of correction to 120 mEq/L.
[c]$P<0.01$ for patients with chronic hyponatremia.
[d]$P=0.003$ for patients with chronic hyponatremia.
[e]$P=0.001$ for patients with chronic hyponatremia.

in hyponatremic emergencies to rapidly correct by about 5 mEq/L (1,2). They differ in recommended regimens and indications for emergency therapy. These differences reflect dissimilar perceptions of whether nonspecific symptoms are life threatening and whether aggressive therapy risks osmotic demyelination in symptomatic hyponatremia.

The European guidelines recommend rapid infusion of 3% saline for severe or moderately severe symptoms without regard to chronicity of hyponatremia (1). "Severe symptoms" were defined as vomiting, cardiorespiratory arrest, deep somnolence, seizures, or coma. Believing all of these to be life threatening and a more serious concern than osmotic demyelination, the group strongly recommended giving an infusion of two 150-ml boluses of 3% saline each over 20 minutes, measuring serum sodium between infusions, and repeating this regimen if necessary to correct by 5 mEq/L. "Moderately severe symptoms" were defined as nausea without vomiting, confusion, or headache. To avoid a spontaneous fall in sodium that could worsen cerebral edema, a single 20-minute, 150-ml infusion of 3% saline was strongly advised for moderately severe symptoms or documented acute hyponatremia (<48 hours). The panel's belief (offered without evidence) that vomiting is a severe symptom requiring emergency therapy, regardless of chronicity, can be questioned. Recent large observational studies report vomiting in approximately one third of hospitalized patients with chronic hyponatremia (Table 3); failure to treat nausea, vomiting, or confusion with 3% saline has not been shown to affect outcomes (47–49). Spontaneous worsening of hyponatremia can occur in acute water intoxication due to delayed absorption of ingested water and in acute postoperative hyponatremia due to excretion of isotonically administered sodium in a hypertonic urine ("desalination") (5); it is unlikely to occur in patients admitted from home who have not yet received intravenous fluids.

The American expert panel also recommended aggressive therapy with 3% saline for seizures and coma, regardless of known chronicity; a 10-minute infusion of 100 ml of 3% saline repeated three times as needed (a regimen borrowed from consensus guidelines for exercise-associated hyponatremia) was recommended (2). The panel acknowledged that, in some settings, nonspecific symptoms, like headache, nausea, vomiting, or confusion, can rapidly progress to seizures, respiratory arrest, and ultimately, death from cerebral edema (22). Therefore, the emergency regimen was recommended

Table 3. Symptoms in patients admitted with hyponatremia

Findings	Author (Ref.), Year		
	Chow *et al.* (47),2004	Arampatzis *et al.* (49), 2012	Nigro *et al.* (48), 2015
Selection criteria	Serum Na<130 mEq/L Thiazide induced	Serum Na <121 mEq/L ED admission	Serum Na<125 mEq/L 46% admit for sx's 96% chronic
No. of Patients	223	168	298
Serum Na mean	116 mEq/L	121 mEq/L	120 mEq/L
Serum Na range	98-128 mEq/L	97-121 mEq/L	IQR 116-123 mEq/L
Confusion	17%	20%	30%
Nausea		38%	44%
Vomiting	35%		30%
Headache		19%	27%
Seizures	0.9%	16%	5%
In-hospital mortality	0%	13%	5%
Fatal cerebral edema	0%	0%	0%
osmotic demyelination syndrome (MRI diagnosis)	One case[a]	0%	0%

Na, sodium; ED, emergency department; sx's, symptoms; IQR, interquartile range, MRI, magnetic resonance imaging.
[a]Serum Na 101 corrected to 116 mEq/L after 36 h, K.M. Chow, personal communication

for symptomatic patients with self-induced acute water intoxication (acute psychosis or schizophrenia, endurance exercise, or "Ecstasy use"), patients with acute postoperative hyponatremia, and patients with intracranial pathology. For others with mild to moderate symptoms, 3% saline at 0.5–2 ml/kg per hour to correct by 4–6 mEq/L was recommended (2).

Therapeutic Limits

Both European and American guidelines distinguish between therapeutic goals (desirable correction rates) and therapeutic limits (rates associated with harm that should be avoided); their goals and limits differ slightly, particularly when the risk of osmotic demyelination syndrome is high. These differences reflect dissimilar conclusions about how often osmotic demyelination syndrome occurs.

In a literature review of series published after 1997, the European panel identified only 54 patients with osmotic demyelination, with mostly poor data on correction rates (1). By comparison, in a survey limited to series published after 2001 with five or more patients, Singh *et al.* (40) found 220 patients with imaging- or autopsy-confirmed osmotic demyelination; at least three quarters were hyponatremic, mostly with serum Na <120 mEq/L. However, correction rates were not analyzed. In 1994, Lohr (50) identified 135 patients with osmotic demyelination syndrome associated with serum sodium ≤126 mEq/L; his review included data on 12 patients who were hypokalemic with available sodium values for the first 24 and 48 hours (Figure 3). Data on 24- and 48-hour correction rates for 85 additional patients can be found in large single-center series published after 1993 (Table 1) and hundreds of single-patient reports (33–38). In addition, a recently published series reported 4 cases of osmotic demyelination syndrome among 1450 patients with Na <123 mEq/L who were admitted to two academic hospitals in Toronto, Canada between 2004 and 2014. All 4 cases had at least 1 additional risk factor for osmotic demyelination syndrome beyond overcorrection of hyponatremia. Correction rates could not be determined in one of these cases whose serum Na was <100 mEq/L. Among the remaining 3 cases, 2 had exceeded the correction limit of 8 mEq/L per 24 hours, and none had exceeded correction limits for average-risk patients (51).

The European panel recommended a 10-mEq/L first day limit and an 8-mEq/L daily limit thereafter (1). The American expert panel recommended the same limits with a daily correction goal of 4–8 mEq/L for patients whose risk of osmotic demyelination syndrome is low (2). For patients at high risk for osmotic demyelination syndrome (serum Na ≤105 mEq/L, alcoholism, malnutrition, hypokalemia, or liver disease), an 8-mEq/L limit and a 4- to 6-mEq/L goal

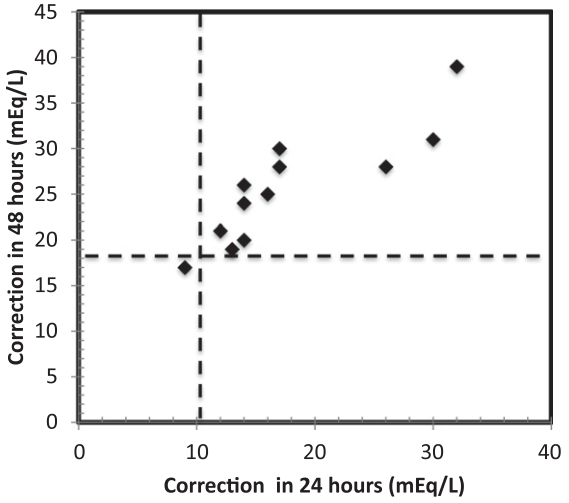

Figure 3. | Most, but not all patients with osmotic demyelination associated with both hypokalemia and hyponatremia and documented by autopsy or magnetic resonance imaging had undergone correction by >10 mEq/L in 24 hours and >18 mEq/L in 48 hours. Patients were identified by a literature review, and they were included if data on sodium correction in the first 24 and 48 hours were provided. Dashed lines represent proposed limits of 10 mEq/L in 24 hours and 18 mEq/L in 48 hours. Modified from ref. 50, with permission.

Table 4. Recommended treatment of symptomatic or severe (sodium ≤120 mEq/L) hyponatremia

Condition	Associated Symptoms	Risk of Morbidity and Mortality from Cerebral Edema	Risk of Osmotic Demyelination Syndrome	Therapeutic Goal and Strategies to Achieve Goal	Therapeutic Limit and Strategies to Limit Correction
Seizures and coma in any patient with serum Na <128 mEq/L Severity of cerebral edema and risk of herniation varies Aggressive therapy indicated regardless of risk of herniation to relieve symptoms and avoid morbidity			Variable depending on chronicity, serum Na level, and comorbidities	4–6 mEq/L within 1–2 h with bolus infusions of 3% saline	Variable depending on chronicity, serum Na level, and comorbidities
High risk comorbidities for osmotic demyelination syndrome Serum Na ≤105 mEq/L Alcoholism or severe malnutrition Hypokalemia or hypophosphatemia Advanced liver disease			High	Variable initial therapy depending on symptoms; 4–6 mEq/L per day	8 mEq/L per day; prevent excessive water losses with desmopressin
Acute hyponatremia from self-induced water intoxication or parenteral fluids or hyponatremia with intracranial pathology	Mild or moderate (nausea, vomiting, confusion, lethargy, or headache)	Considerable risk of herniation and morbidity from aspiration or hypoxia	Low	4–6 mEq/L within 1–2 h with bolus infusions of 3% saline	10 mEq/L in first 24 h and 8 mEq/L daily thereafter; replace water losses or prevent water losses with desmopressin
Chronic severe hyponatremia (Na≤120 mEq/L) without high-risk comorbidities	Moderate (nausea, vomiting, confusion, lethargy, or headache)	Minimal risk of herniation but risk of morbidity from falls or seizures	Variable depending on level of serum sodium concentration	4–6 mEq/L within 6–12 h with infusion of 3% saline with or without a bolus	8 mEq/L per day; replace water losses or prevent water losses with desmopressin
Chronic severe hyponatremia without high-risk comorbidities	Mild or asymptomatic	No risk of herniation but risk of morbidity from falls	Variable depending on serum sodium concentration	4–8 mEq/L within 24 h	8 mEq/L per day; replace water losses or prevent water losses with desmopressin

Na, sodium.

were recommended for these reasons: excessive correction on any day, not just the first or second day, can cause osmotic demyelination syndrome; osmotic demyelination syndrome has been reported after correction by 9 mEq/L per day; correction by 4–6 mEq/L seems adequate, even with severe symptoms; there is no evidence that the first day's correction should be greater than on other days; and there is a risk of inadvertently overshooting the mark (2,3,7,49,52) (Figures 1–3, Tables 1–3).

On the basis of convincing animal data (15), the European and American panels both endorsed therapeutic lowering of serum sodium for inadvertent excessive correction, despite the absence of documented benefit in humans, noting that patients tolerate the maneuver (53).

Future Research

A prospective, randomized trial, registered in August 2016, will compare European bolus regimens with slow infusions of 3% saline in patients with moderately severe or severe symptoms (54). Results should be available in 2 years. The study is unlikely to detect differences in the incidence of fatal cerebral edema, because it is rare. However, it should be possible to determine if the bolus regimen is more effective in preventing or terminating seizures and to compare likelihoods of overcorrection. Urea can increase serum sodium and is now available as a medical food (ure-Na.com) (55). A trial comparing oral urea to slow 3% saline infusion in patients who are chronically hyponatremic with moderate symptoms would be helpful.

Currently, accepted limits are primarily derived from small cohorts with serum sodium ≤105 mEq/L (6,17,18). A larger, multicenter, multiyear, retrospective, observational study is needed. Osmotic demyelination syndrome is sufficiently common at sodium levels ≤105 mEq/L to test the validity of proposed limits, confirm the safety of very slow correction, and explore outcomes after therapeutic relowering. Mild osmotic demyelination syndrome may escape detection, even with careful chart review. A prospective study of patients with

serum sodium ≤105 mEq/L correlating serial psychomotor tests and neurologic examinations with correction rates would help further define therapeutic limits.

While awaiting additional data, physicians already know enough to manage hyponatremia sensibly (Table 4). Even if morbidity and mortality from untreated hyponatremia are rare, the fact that they occur justifies aggressive but limited correction of acute hyponatremia or severe symptoms. Similarly, even if therapeutic complications are uncommon, there is no reason to risk them by correcting hyponatremia by more than necessary.

Disclosures

None.

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